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Schizophrenia

Nicholas Meyer BM BCh MRCPsych is Clinical Research Fellow at the Institute of Psychiatry, Psychology and Neuroscience, King's College London, and South London and Maudsley NHS Foundation Trust, UK. Competing interests: none declared. Contact address: Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, London SE5 8AF. email: nicholas.meyer@kcl.ac.uk

James H MacCabe MBBS MRCPsych MSc PhD is Reader in the Epidemiology of Psychosis at the Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK and Consultant Psychiatrist, National Psychosis Unit, South London and Maudsley NHS Foundation Trust. Competing interests: none declared. Contact address: Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, London SE5 8AF. email: james.maccabe@kcl.ac.uk

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Abstract

Schizophrenia is a common and severe mental illness affecting several domains of cognition and behaviour. The illness most frequently becomes manifest in early adulthood, and often follows a chronic course. It is associated with high morbidity and mortality, and is a leading contributor to disease burden, health and social care costs throughout the world.

Antipsychotics are the mainstay of treatment but are limited by significant adverse effects, and therapeutic options for many patients remain inadequate. Schizophrenia is associated with a range of adverse physical health outcomes, which may be compounded by lifestyle factors including substance use, barriers in accessing healthcare, and the adverse effects of treatment. Psychological and social interventions are a crucial element of patient care, particularly in alleviating negative symptoms.

Current theories view schizophrenia as a disorder of early brain development with interacting genetic and environmental risk factors.

Keywords

psychosis; schizophrenia; delusion; hallucination; antipsychotic; dopamine

Definition

Schizophrenia is a mental illness characterized by positive symptoms (delusions, hallucinations, thought disorder and disorganised behaviour), negative symptoms (social withdrawal and apathy) and cognitive symptoms (poor executive function and memory). It frequently follows a chronic course and is associated with a decline in social and occupational functioning. ICD-10 criteria for schizophrenia are listed in table 1, and require a symptom duration of at least one month.

Epidemiology

The prevalence and incidence of schizophrenia vary widely depending on the location and the diagnostic definition that is employed. Whilst it is often quoted that 1 in 100 of the population will have schizophrenia in their lifetime, studies suggest that the global average lifetime prevalence is somewhat lower, at 0.72%¹. In a study of incidence of schizophrenia in England from 1997 to 1999, the age-adjusted incidence in Bristol was 7.2, Nottingham 7.6, and SE London 20.1 cases per 100,000 person-years suggesting geographical heterogeneity in underlying biological, psychological and environmental risk factors. The average general practitioner can expect to see around one new case per year, and have between five and 10 patients with the diagnosis on their caseload.

Schizophrenia usually emerges in late adolescence or early adulthood, with women having a later average age of onset compared with men. Onset is rare before the age of 16, and uncommon after the age of 50.

Pathophysiology

The *dopamine hypothesis* has played a central role in neurobiological theories of schizophrenia. Support comes from the observation that drugs such as amphetamines, which stimulate dopamine release, can induce psychosis, and that all antipsychotic drugs exert antagonism to D2 dopamine receptors, with the degree of antagonism correlating with the therapeutic dose. PET and MRI ligand studies have demonstrated increased presynaptic dopamine synthesis and release during acute psychosis. However, approximately a third of patients show a limited response to antipsychotic treatment, and recent findings suggest that this subgroup may not exhibit dopaminergic dysfunction.

MRI studies have shown an overall decrease in brain volume of 3–4%, with particular differences in the volume of the hippocampi and thalamus, and enlargement of the lateral ventricles. At a cytoarchitectural level, an absence of gliosis and other correlates of cell injury or death strongly argue that schizophrenia is not due to a neurodegenerative process.

Aetiology

A concept that has gained widespread currency is the *neuro-developmental hypothesis* of schizophrenia, which proposes that although the overt phase of illness is usually of adult onset, its roots lie in the preceding stages of brain development. The pathogenesis of schizophrenia is considered to be dependent upon the interplay between genetic vulnerability, environmental and social factors².

Genetic vulnerability

Monozygotic twin concordance rates for schizophrenia of about 50% point to a significant genetic basis, and current estimates suggest an overall heritability of around 80%. Nonetheless, most individuals who have been diagnosed with schizophrenia have no family history of psychosis, and no single genes have been identified, suggesting that many risk alleles of small effect size are involved. A landmark genome-wide

association study (GWAS) identified 108 loci conferring risk for the disorder³, with notable associations with the *DRD2* dopamine-receptor gene and the major histocompatibility complex (MHC) coding region, suggesting a role for the immune system in schizophrenia. A recent study provided further support for this hypothesis by demonstrating specific associations with the C4 complement gene and schizophrenia risk.

Polymorphisms in genes involved in neuronal migration (*DISC1*), synaptogenesis (neurexin family), and glutamate transmission (*GAD67/GAD1*) have also received attention. New techniques that are able to detect deletions and duplications of chromosomal segments, known as *copy number variants* (CNVs), have revealed an over-representation of CNVs in schizophrenia, particularly in regions carrying genes involved in neuronal development. Recent studies have also demonstrated a shared genetic liability for schizophrenia and bipolar disorder, suggesting an aetiological continuum between the disorders.

Gestational and perinatal exposures

A wide variety of prenatal exposures, such as viral or bacterial infection, stress and malnutrition, and perinatal variables, such as low birth weight, prematurity, prolonged labour and neonatal hypoxia, have demonstrated associations with an increased risk of schizophrenia. An intriguing finding is the modest but consistently raised incidence of schizophrenia among individuals born in winter months, which may be causally related to seasonal variation in rates of intrauterine viral infection.

Urbanicity, immigration and social adversity

Urban upbringing is associated with a more than 2-fold increase in risk of schizophrenia compared to rural settings, in a dose-dependent fashion. Various lines of evidence suggest this is not explained by a 'drift effect' of genetically vulnerable individuals moving to an urban setting, but rather to factors related to urban living, such as the physical environment and social disadvantage.

Consistently increased rates of schizophrenia are seen in first- and second generation immigrants above that of non-migrants. It has been shown that the risk of developing schizophrenia is decreased among minority ethnic groups living in areas with a higher density of their own ethnic group, suggesting that the degree to which one occupies a minority position, with the associated experiences of chronic social inferiority and marginalization, might be of aetiological importance.

Substance use

An expanding literature supports the hypothesis that cannabis increases the risk of developing schizophrenia. A systematic review found a dose-dependent increase in risk of long-term psychotic outcomes among those who had ever (odds ratio 1.41) or frequently (odds ratio 2.09) used cannabis. Recent research has identified a three-times excess risk among users of high-potency 'skunk', a form of cannabis containing a greater proportion of the active ingredient, tetrahydrocannabinol, than traditional

marijuana. Amphetamines, LSD, ecstasy and ketamine ingestion have also been implicated in the precipitation of psychotic states.

Clinical features and course

The syndrome of schizophrenia can be divided into *positive* or *negative* symptom dimensions. Additionally, frank onset of illness is often preceded by a sub-clinical *prodromal state*, commonly of several weeks to months' duration, characterized by social and occupational withdrawal, loss of interest in activities, change in personality, altered mood and paranoid ideas. Progression to psychosis and the subsequent mode of presentation to psychiatric services is often with bizarre or disinhibited behaviour, deliberate self-harm or attempted suicide, intoxication, or police involvement.

Positive symptoms are those that are seen during the acute psychotic state, and are characterized by disturbance in a broad range of cognitive functions, including a loss of the normal flow of thinking, usually demonstrated in the patient's speech (formal thought disorder), delusions, often of a paranoid nature, a loss of sense of agency over thoughts and actions (passivity phenomena) and hallucinations, often in the form of hearing voices.

The negative symptom cluster is an enduring aspect, most often interposed between, and co-existing with, episodes of acute psychosis. It reflects a defect state affecting several neurocognitive domains, characterized by impairments in motivation and willed action, blunted and flat affect, anhedonia, poverty of thought and speech, poor self-care and loss of appropriate social interaction. It is a highly disabling aspect of the illness, not least due to its chronicity.

A less overt but equally disabling core feature of schizophrenia is the associated cognitive deficit. Patients with schizophrenia perform on average 0.5-1 standard deviation below controls in a broad range of cognitive domains, with particular deficits in frontal lobe function, attention and processing speed, although 20-30% of patients are cognitively intact. Where cognitive deficits do exist, they appear to be relatively chronic and independent of positive symptoms, and can impact profoundly upon an individual's social and occupational function.

Assessment and diagnosis

There are no reliable pathophysiological markers of schizophrenia, and diagnosis is therefore made clinically through the identification of the characteristic syndrome. The ICD-10 criteria for diagnosis are set out in ([Table 1](#)). ICD-10 and DSM-IV classification systems have historically split schizophrenia into simple, paranoid, hebephrenic and catatonic subtypes, but these have been removed from DSM-5 due to their limited diagnostic stability and clinical utility.

Assessment should begin with a comprehensive psychiatric, medical and social history, and collateral information is often invaluable. Physical examination, including a thorough neurological examination to identify organic pathology, is essential, and cognitive function should be examined where possible. Routine blood tests including baseline

lipid and glycaemic profile are indicated, and an ECG and urine drug screen should be obtained. In a first presentation of psychosis, testing for antibodies against the N-methyl-D-aspartate (NMDA) receptor and voltage-gated potassium channel complex is gaining increasing acceptance. MR imaging and EEG are indicated if an organic cause is suspected. The differential diagnosis for a psychotic presentation is outlined in ([Table 2](#)). Assessment should be made of the patient's level of insight into their illness, capacity to consent to treatment, and risk to self and others, and a plan for hospital admission made accordingly.

Prognosis

Following a first episode of psychosis, reasonable control of psychotic symptoms can be achieved in over 80% of patients, with effective treatment. However, without maintenance antipsychotic medication, more than 90% of patients will relapse, highlighting the critical importance of long-term treatment in improving outcome.

Making accurate predictions about clinical course in individual patients is challenging, and outcomes are highly heterogeneous. Studies after first episodes of psychosis have broadly shown that, with treatment, around 20% of patients will fully recover with a good functional outcome, 35% will experience a relapsing and remitting illness with good function in between episodes, and another 35% will have chronic positive and negative symptoms requiring ongoing community care. Around 10% will suffer severe chronic symptoms, requiring long-term inpatient treatment or residential care, often involving forensic services.

Schizophrenia is associated with a 15-year average reduction in life-expectancy. Suicide accounts for 40% of the excess mortality, with 5–10% of patients eventually dying by suicide. More than half of suicides occur in the first 5 years of illness, making individuals recovering from their first episode of psychosis a particularly high-risk group.

The remaining 60% of the excess in mortality is accounted for by physical health problems⁴. Infectious, cardio-respiratory, metabolic, musculoskeletal, and endocrine disease are more frequent in schizophrenia than in the general population. Though some of these poor outcomes can be explained by behaviours relating to schizophrenia (e.g. smoking and inactivity secondary to negative symptoms) and its treatment with psychotropic medication, a neglected factor is the disparity in healthcare access, utilisation and provision. People with schizophrenia are less likely to receive the same standards of care for physical disorders than individuals without mental illness, a result of stigma and 'diagnostic overshadowing' – the assumption that physical complaints are psychosomatic symptoms arising from mental illness.

Despite this somewhat pessimistic outlook, careful formulation and case management at an individual level, good communication and education with patients and their families, and an emphasis on the importance of continuing to take medication when required can improve considerably quality of life and longer term outcomes.

Management

Schizophrenia can be a bewildering, distressing and stigmatizing illness for patients and their carers, and necessitates a compassionate, multi-disciplinary approach. In the UK, emphasis is placed on managing patients with schizophrenia in the community, with delivery of care by community mental health teams, crisis teams and day hospitals. Where necessary, admission is made to hospital for assessment and treatment, often with compulsion under sections 2 and 3 of the Mental Health Act.

All people with first presentation of psychotic symptoms should be referred urgently for assessment by a secondary care level, local community-based mental health service. Where available, direct referral should be made to services specializing in early intervention in psychosis.

Pharmacological interventions

The goals of pharmacotherapy in schizophrenia are to minimize symptoms and functional impairment, reduce rate of relapse and hospital admission, whilst at the same time keeping adverse effects to a minimum. Antipsychotics are effective in treating positive symptoms, but are at best only partially effective in treating the negative symptoms of schizophrenia. Drugs that block postsynaptic D2 dopamine receptors have formed the mainstay of treatment for schizophrenia; these have traditionally been divided into first generation antipsychotics, such as sulpiride and haloperidol, and newer second generation agents, such as olanzapine and risperidone. Oral short- and long-acting (depot) injection preparations are available in both groups, and are generally reserved for cases where adherence with oral medication is poor.

First generation agents primarily exert antagonism at the D2 receptor together with antagonism at muscarinic cholinergic, histaminergic and α -1 adrenergic receptors, whereas second generation antipsychotics have a broader receptor profile, antagonizing central serotonergic receptors as well as blocking a range of dopamine receptors more weakly. Their adverse-effect profiles are therefore different, with first generation drugs tending to cause troublesome *extrapyramidal effects* (EPSEs) such as dystonia, bradykinesia and akathisia, through blockade of nigrostriatal D2 receptors. Second generation antipsychotics cause fewer motor adverse effects, but predispose to the *metabolic syndrome*, including weight gain, dyslipidaemia, hyperprolactinemia and glucose intolerance. Treatment with any antipsychotic drug therefore often comes at a significant cost. Common adverse effects associated with antipsychotic treatment are set out in the article on Antipsychotics in Psychiatry II (*Medicine xxx, xxx*).

Large randomized controlled trials comparing first and second generation antipsychotics have challenged the belief that second generation agents are more effective at treating the positive and negative symptoms of schizophrenia. The CATIE (USA) and CUtLASS 1 (UK) trials demonstrated lack of superiority of second generation over first generation agents in terms of symptom and quality-of-life scores. A recent meta-analysis⁵ illustrates however that although antipsychotics show only small differences in efficacy, they differ substantially in their propensity to cause side-effects that lead to treatment

discontinuation, and reinforces how choice of treatment should be tailored to the needs of the individual patient.

Around 30% of patients fail to respond significantly to two or more antipsychotics, and are therefore considered to have 'treatment-resistant' illness. 30-50% of treatment – resistant patients will respond to clozapine, making it an important and unique second-line treatment. However, 0.5–1% of patients develop potentially fatal clozapine-induced agranulocytosis; registration with a monitoring service and monthly blood testing is therefore mandatory for patients receiving clozapine. Other serious and often overlooked side-effects include aspiration pneumonia, neuroleptic malignant syndrome (NMS), ileus and myocarditis.

Social and psychological interventions

Modern community services for patients with schizophrenia are organized with the aim of providing treatment and rehabilitation through the use of case management (care programme approach or CPA) and assertive community treatment services. Assisting patients in finding appropriate accommodation, and working to promote education and supported employment are key goals of these agencies.

Family therapy aimed at educating relatives about the illness and its management, and altering attitudes and behaviour relating to it, is recommended by NICE for all patients with schizophrenia.

Emerging evidence points to the utility of combining medication with psychological interventions, particularly cognitive behavioural therapy (CBT) and family interventions, in improving clinical outcomes. In particular, CBT has been shown to lead to long-term reduction in the intensity and distress associated with treatment-resistant delusions and hallucinations. There is also evidence for use of psychological treatments in improving medication adherence and preventing relapse.

Key points

- Schizophrenia is a complex and chronic illness requiring a co-ordinated multi-disciplinary approach.
- Early referral and treatment should be established in first presentation of psychosis.
- Oral antipsychotics should be offered following a discussion with the patient of the relative risks and benefits. Polypharmacy should be avoided, and medication should be continued at the lowest effective dose.
- Cognitive behavioural therapy should be offered to all patients, and family therapy to relatives of people with schizophrenia.
- Mortality in schizophrenia is twice that of the general population; co-morbid physical illness is over-represented as a result of lifestyle factors, effects of medication, and requires recognition and treatment.
- Individuals with schizophrenia should be treated in a non-judgemental and compassionate manner, with emphasis on promoting recovery and reducing stigma amongst patients, carers and the public.

Table 1: ICD-10 criteria for schizophrenia (F20)^a

- At least **one** of the following:
 - Thought echo, thought insertion or withdrawal, or thought broadcast
 - Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception
 - Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body
 - Persistent delusions of other kinds that are culturally inappropriate and implausible (e.g. being persecuted by a network of government agents; being an emissary from another world)
- **Or** at least **two** of the following:
 - Persistent hallucinations in any modality, when occurring every day for at least a month, when accompanied by fleeting or half-formed delusions without a clear affective component, or when accompanied by persistent over-valued ideas
 - Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech
 - Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor
 - Negative symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses
- Duration of the above symptoms for **at least 1 month**.

^a ICD-10 classification of mental and behavioural disorders, diagnostic criteria for research.¹⁴

Table 2: Differential diagnosis for psychotic episode (more common diagnoses listed first)

| Functional | Organic |
|--|---|
| Affective psychosis (mania or depression with psychotic features) (F30–39) | Delirium, including alcohol withdrawal state and metabolic or endocrine derangement |
| Schizo-affective disorder (F25) | Medication-induced psychosis (including corticosteroids, antihistamines, dopamine agonists, sympathomimetics) |
| Substance-induced psychotic disorder (including alcohol, stimulants, hallucinogens) (F10.5–19.5) | Autoimmune encephalitis (e.g. VGKC and NMDA receptor antibody mediated) |
| Persistent delusional disorder (F22) | Neurodegenerative conditions (e.g. Alzheimer's disease, Wilson's disease) |
| Acute transient psychotic disorder (F23) | Epilepsy: post-ictal and inter-ictal psychosis; particularly temporal lobe seizures |
| Schizotypal personality disorder (F22) | Brain injury |
| Paranoid personality disorder (F60.0) | CNS neoplasm |
| Induced/shared psychotic disorder (<i>folie a deux</i>) (F24) | CNS infection (e.g. neurosyphilis, HIV seroconversion, herpes encephalitis) |
| Factitious disorder (F68.1) | Systemic lupus erythematosus |
| | Multiple sclerosis |

CNS, central nervous system; HIV, human immunodeficiency virus; NMDA, N-methyl-D-aspartic acid; VGKC, voltage-gated potassium channel.

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